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**A systematic review of the definitions of Vascular Cognitive Impairment-No Dementia
(VCI-ND) in cohort studies.**

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Author statement

All authors have read the paper and agree to be listed as authors

Conflicts of interest

None

Abstract

Background/Aims No set operational criteria for Vascular Cognitive Impairment-No Dementia (VCI-ND) have yet been established. The aim of this study is to undertake a systematic review to compare definitions of VCI-ND that have been used in cohort studies.

Methods Medline, PsychINFO and Embase were searched from inception to October 13, 2015. 3,142 records were initially screened, and 30 were included in this review.

Results No single set of criteria for defining VCI-ND was identified. VCI-ND was broadly defined as an absence of dementia, cognitive impairment in at least one cognitive domain with signs of vascular involvement, and intact activities of daily living.

Conclusion Defining criteria will enable individuals with VCI-ND to be efficiently compared across cohort studies to more accurately determine prevalence and risk of dementia.

Introduction

The concept of Vascular cognitive impairment (VCI) was developed to identify individuals who have impaired cognitive function beyond that seen with the ‘normal’ aging process and which occurs in the presence of underlying age-related vascular pathology [2-5]. The American Heart Association and American Stroke Association guidelines have suggested that VCI should include all states of cognitive impairment associated with a vascular disorder, from very mild levels of impairment to evident dementia [4]. However, these underlying states are very diverse and a need has been identified to further define the different levels of cognitive impairment encompassed within VCI. Updated criteria for dementia have identified the need to separate mild neurocognitive disorders from major neurocognitive disorders, which included those of vascular aetiology. Vascular Cognitive Impairment-No Dementia (VCI-ND) has been developed as a concept to capture individuals who are at the earliest stage of VCI and who may be at a higher risk of developing further cognitive decline and dementia [6]. VCI-ND is thought to be a pre-dementia state, yet while some individuals may go on to develop further cognitive decline or vascular dementia (VaD), others may return to a ‘normal, healthy’ state of cognitive function [7]. The differences in progression rates to dementia between individuals with VCI-ND may be due to inconsistencies in the operationalization of VCI-ND across studies including: whether individuals with pure or mixed (e.g., with Alzheimer’s disease) pathology are included in the definition; differences in the underlying causes of the vascular pathology, such as large or small vessel diseases leading to ischaemic strokes, white matter lesions, hypoperfusion or haemorrhage [8]; and, the cognitive domains investigated.

The aim of this review is to summarise how the current literature has defined VCI-ND within cohort studies in order to enable comparisons of the prevalence of VCI-ND in different populations and the risk of developing dementia.

Methods

Selection criteria and search strategy

This systematic review was undertaken in accordance with the 2009 PRISMA statement [9]. Medline, PsychINFO and Embase were searched from inception until October 13, 2015. The search strategy is shown in the supplementary material. The search was limited to articles published in English and studies involving humans. One author completed the electronic search (SLH).

Articles were included if they examined VCI-ND or vascular mild cognitive impairment (MCI) i.e. cognitive impairment without dementia due to vascular pathology, and had a cohort study design, though they did not have to present follow-up data. There was no restriction on sample age. Articles were excluded if they combined individuals with VCI-ND and individuals with dementia to form a VCI group, and/or they did not use the terms VCI-ND or vascular MCI (e.g., if they only used the terms post-stroke cognitive impairment or CIND). Two authors (SLH and EYHT) independently searched the article titles and abstracts. When a title/abstract of a study could not be rejected with certainty, the full text was obtained for further investigation. The full text articles were then retrieved and assessed for eligibility. Relevant reviews examining VCI-ND were also obtained and the reference lists of these and each included paper were examined for any missed articles. Any discrepancies between the selections made were resolved by consensus or by asking a third investigator (BCMS).

Data extraction

Two authors (SLH and EYHT) independently extracted data which included: author, date of publication, participants (cohort (e.g., stroke cohort), country), demographics (age, gender distributions), prevalence of VCI-ND (by any sub-groups e.g., age, sex), and study-specific operationalization of VCI-ND including the vascular component, neuropsychology measure

(including test and domain reflected, as described in the articles or from appropriate literature [10]) and activities of daily living (ADL). Discrepancies between data extraction results were resolved by review of the two authors (SLH and EYHT). The quality of the included studies was not assessed and a meta-analysis was not conducted, as these were not relevant to this review.

Results

Main Search

The search identified 5,520 publications, of which 3,142 were unique. After screening titles/abstracts, 63 publications were retained for full-text review of which 30 publications met the inclusion criteria (see Figure 1). Supplementary Tables 1 and 2 provide detailed descriptions of the articles included in this review.

Study Characteristics

Cohorts were either population based (n=8) [11-18] (primary care), hospital-based (general secondary care) (n=7) [19-25], specialist centres (tertiary care based, referred by a specialist clinic (e.g., memory, cardiovascular hospital clinic) (n=14) [26-38] or mixed research centre and hospital-based (n=1) [39]. Many studies only included individuals above a certain age (e.g., ≥ 45 years [39], ≥ 65 years [11-16,18,34] or ≥ 75 years [17,20,25]). Fourteen studies were based on populations with a previous history of stroke [19-28,37-40].

Defining VCI-ND in the cohort studies

The criteria used to define VCI-ND varied widely (Table 1). Where studies did employ similar/the same criteria they were generally conducted on the same sample or by the same authors. Variability was found in the cognitive domains included, the cognitive tests applied, the degree of cognitive impairment, the vascular component of VCI-ND and whether impairments of ADLs were part of the definition and how they were measured..

Criterion 1: Exclusion of individuals with dementia

The most commonly used criteria for dementia case exclusion were the Diagnostic and Statistical Manual of Mental Disorders (DSM)-III-revised [11,12,14,16,18,20,25,31,32,34-36] or the DSM-IV criteria [13,15,21,22,28,38-40]. Also used were the Clinical Dementia Rating (CDR) of 1+ [17], medical history [26,27], clinical diagnosis [29,30] and Mini Mental State Examination (MMSE) score ≤ 21 [33], or, in the case of one study, below the second

percentile on the Korean MMSE [21]. Six studies excluded individuals using criteria for VaD [19,33,37,38] .

Criterion 2: Cognitive impairment

The majority of studies (n=28) used a definition that included impairment in at least one cognitive domain or impairment of global cognitive function [13,15,20,26,34] (in studies which looked at individual cognitive domains up to thirteen cognitive domains were assessed) [23,24]. Two studies stated cognitive impairment must be present in executive function and memory [29,30]. Two studies stated cognitive impairment could be definitive impairment in one cognitive domain or marginal impairment in two cognitive domains [23,24] (Supplementary Table 2). In five studies only global cognitive function was assessed rather than individual domains [13,15,20,26,34], including one which used two different tests (MMSE and Montreal Cognitive Assessment (MoCA)) and further defined VCI-ND as *VCI-ND mild* (either MMSE ≤ 24 or MoCA ≤ 21) or *VCI-ND moderate* (both MMSE ≤ 24 and MoCA ≤ 21) [26]. Another study also described VCI-ND as mild or moderate, but used a different classification for this: mild defined as cognitive impairment present in ≤ 2 cognitive domains or moderate defined as cognitive impairment present in ≤ 3 cognitive domains [27].

Criterion 3: Vascular component

Fourteen studies were conducted in populations with a recent stroke with the majority (n=12) assuming that cognitive impairment was due to this recent stroke and therefore vascular-related. One study however, stated that a vascular cause was only given if there was an absence of pre-stroke cognitive impairment [22]. The Sydney Stroke Study used clinical and neuroimaging data to define the vascular component of VCI-ND by evidence of cerebrovascular disease on MRI or CT scan clinically judged to be sufficient to account for cognitive impairment [23,24]. Other studies relied on clinical signs of vascular involvement (e.g., neuroimaging data for evidence of white matter lesions or large/small vessel ischaemic

changes in the brain) [13-15,17,29,30,33,34], previous vascular or cerebrovascular disease (stroke, atherosclerosis or other cerebrovascular disease) [16,18] or a combination of clinical signs and history of cerebrovascular disease or vascular risk factors [11,12,31,32] (Supplementary Table 2).

Criterion 4: Physical function

ADL or functional impairments were included as part of their criteria for defining VCI-ND in 23 studies although these differed in the level of ADL impairment acceptable for defining VCI-ND, as well as how ADLs were assessed (Supplementary Table 2).

Prevalence of VCI-ND

The proportion of participants with VCI-ND in each study varied from 24% [25] to 75% [40] in stroke-only populations, and 4% [16] to 19% [31] in populations where stroke prevalence was low or not reported. Some studies (n=4) [26-28,39] also reported variable criteria and prevalence rates for different types of VCI-ND (e.g., mild or moderate, amnesic or non-amnesic, single domain or multiple domain) which ranged from 3% to 41% depending on the classification of VCI-ND [28] [39] [27] [26], and one study used more than one definition to compare prevalence rates of VCI-ND (range 10% to 50% depending on definition) [21].

Progression of VCI-ND over time

Seven studies investigated progression of patients with VCI-ND and reported changes in cognitive function or incident dementia rates [12,15,23,29,31,37,40], though the length of follow-up varied as well as whether cognitive test scores or dementia rates were examined over time, thus making comparison difficult (Table 2).

Developing new VCI-ND criteria

The results of this review and information from previous VaD criteria and criteria for MCI due to AD [1] have been used in order to develop a “strawman” proposal for VCI-ND criteria in research settings (Box 1). These criteria have been proposed to promote debate and for

researchers to begin discussing how VCI-ND criteria should be developed and these will provide a foundation for standardised criteria to be developed.

Discussion

This review highlights that while there is a broad consensus in cohort studies regarding a definition for VCI-ND (i.e. people who are free from dementia, have cognitive impairment that is thought to be due to a vascular cause and have relatively preserved ADLs), there is a lack of consistent operational criteria, specifically: (1) classifying dementia status; (2) evidence of cognitive impairment; (3) defining the vascular origin of cognitive impairment; and, (4) the use of functional disability in the definition. This makes it difficult to compare results across studies and could be a major reason for the wide variance in prevalence estimates (range 4% to 19% in non-stroke cohorts and 24% to 75% in stroke-only cohorts), as well as the risk of dementia.

The area with most variability was the definition of cognitive impairment. The majority of studies agreed that cognitive impairment should be present in at least one domain and that both fluid (e.g., speed, attention) and crystallized abilities (e.g., verbal knowledge, abstraction) should be assessed. Global cognitive function was also measured in some studies using the MMSE or MoCA. When assessing global cognitive function, the MoCA may be more useful than the MMSE for detecting cognitive impairment particularly in early stages of VCI [41]. Previous research has suggested that fluid abilities (e.g., information processing speed) may be more vulnerable to cerebrovascular dysfunction than crystallised abilities, at least at non-severe impairment stages [7,42]. Therefore VCI-ND prevalence rates may be higher if the definition of VCI-ND includes impairment of fluid abilities. Studies should investigate VCI-ND in a more systematic manner by using multiple domain-specific cognitive measures, as well as a global cognitive measure and recording disease duration. The underlying vascular component was not consistently evaluated across studies and an important consideration is the role and limitations of neuroimaging in this. Not all studies included neuroimaging data when deciphering if the underlying cause of the cognitive

impairment was vascular, and those that did differed as to how the neuroimaging data were interpreted. Some studies did not distinguish between small or large vessel disease, despite there being differences in the effect on cognitive function. Specifically large vessel disease may result in cognitive and other deficits that depend on the location of the infarcts, but small vessel disease may only affect certain cognitive domains such as attention, information processing speed and executive function [43]. Recently, criteria have been proposed for the condition termed MCI due to AD [1]. Similarly to VCI-ND, MCI due to AD requires individuals to have cognitive impairment in at least one cognitive domain, be free from dementia and preservation of ADLs. Therefore, the deciding factor in distinguishing between VCI-ND and MCI due to AD will be the determination of the underlying aetiology of the cognitive impairment.

It is important to note that dementia and pre-dementia states may not always have a single cause. Indeed, late-life dementia is highly unlikely to have a single cause (but rather be mixed including Alzheimer's and vascular pathology) and it is not always clear as to the underlying source of the cognitive impairment [44]. This would create difficulty in classifying these individuals and we would suggest that a new term for these individuals would be required, such as CIND with AD and vascular pathology.

In order to develop operational criteria for VCI-ND, future research should use the evidence gathered in this review and in previous studies examining definitions of VCI-ND [45] and MCI [1], but this needs to be accepted with the caveat that frequently dementias are mixed. Studies should, where feasible, exclude other possible causes of cognitive impairment such as Parkinson's disease or MCI due to AD. A wide range of cognitive domains should be investigated and cut-offs for impairment should be age and education adjusted. Impairments of episodic memory are characteristic of MCI due to AD, and therefore such cases should be thoroughly investigated for signs of AD, such as amyloid-beta plaques and neurofibrillary

tangles [1]. ADLs should also be considered in relation to a person's age and what is considered normal for their age; and further within the context of the severity of cognitive impairment (e.g., problems with managing money or managing medications will be affected by severe cognitive impairment). After ruling out other causes of cognitive impairment, recent cardiovascular events (e.g., stroke) should be considered as possible underlying causes of VCI-ND. To identify probable VCI-ND information on cognitive status prior to cardiovascular events is needed to confirm that cognitive impairment was absent prior to the cardiovascular event. Alternatively, cerebrovascular lesions, as determined by neuroimaging, should be identified, although there is also likely to be different causes for vascular lesions (e.g., hypotensive episodes for white matter lesions) and therefore the defining criteria for the vascular lesion component of VCI-ND may necessitate classification subdivisions. Further subdivisions based on aetiology may enable more accurate prognosis and assist with management of the condition.

A consensus statement for operational criteria for VCI-ND is needed. The results of this review and information from previous VaD criteria and criteria for MCI due to AD [1] have been used in order to develop an informal proposal for VCI-ND criteria in research settings (Box 1). These criteria have been proposed with the aim of helping to develop future VCI-ND guidelines, not to be definitive operational criteria.

Two different sets of criteria have been previously proposed for MCI due to AD, the first designed to for healthcare providers in a wide range of clinical settings, and the second designed for clinical research settings with access to advanced neuroimaging options [1]. Similar to MCI due to AD, two main sets of criteria could be developed for VCI-ND: an accessible version for healthcare settings that focusses on clinical features for diagnosis and does not involve advanced investigative approaches as well as a more detailed and specific set of criteria for clinical trials based on advanced neuroimaging approaches and other

biomarkers. Such an approach would enable the classification of possible and probable VCI-ND based on the extent of vascular injury observed and the extent of any comorbid pathology which is present such as AD. Large cohort studies will be required to determine usability and iteratively develop these criteria.

The main strength of this study is that it is the first systematic review undertaken to examine how the concept of VCI-ND has been defined in different cohort studies. There are some limitations to this review. We chose to only examine cohort studies, as we were interested in the operationalization of VCI-ND defining criteria and comparing population prevalence of VCI-ND across studies. We excluded studies that did not specifically describe VCI-ND or vascular MCI. There is the possibility therefore that we have excluded papers due to a difference in terminology as cognitive impairment associated with vascular disease may not have always been termed VCI-ND, but the focus of the review was on this concept explicitly. Many of the included studies were based on the same datasets (such as CSHA [11,12,14,16,18] and CIVIC [32,35,36]). In addition, there were few truly representative population studies with most studies being hospital-based or stroke-only populations, limiting the generalizability of the results.

Summary

Our results highlight the ongoing difficulties in mapping VCI-ND without a standard protocol or set definition. In order to fully understand the prevalence of VCI-ND and risk of dementia associated with the condition in different populations, agreement on the specific operational criteria of VCI-ND must be reached. Identifying patients with VCI-ND before they are at a stage where cognitive impairment is too severe is important as it may be early enough to offer secondary prevention strategies. Differentiating between the underlying vascular causes of cognitive impairment in VCI-ND, although not always straightforward, will be useful for initiating appropriate intervention strategies. That some studies find improvement in

proportions of people with VCI-ND should motivate inquiry into ways in which some people appear to improve, and which factors most favour improvement.

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Figure legends

Figure 1. PRISMA flow chart of the literature search.

Tables

Table 1. Criteria for VCI-ND and the differences found between studies in operationalising the criteria

VCI-ND criteria	Differences between studies
Free from dementia	Different criteria including: DSM versions III-Revised and IV, CDR, clinical diagnosis, medical history, MMSE or criteria for VaD (NINDS-AIREN or “definite impairment in two or more cognitive domains (impairment in memory was not necessary), evidence of functional decline, evidence of cerebrovascular disease by neuroimaging and clinical data”)
Cognitive impairment in at least one cognitive domain	Cognitive domains included, cognitive tests used and cut-off scores for impairment (Note: two studies defined VCI-ND as cognitive impairment in 2 or more cognitive domains)
Vascular component	Presence/absence of previous stroke (clinical diagnosis) or vascular history (previous stroke, atherosclerosis or other cerebrovascular disease) or whether consideration was given to clinical signs using neuroimaging data (e.g., evidence of cerebrovascular disease on MRI or CT scan clinically judged to be sufficient to account for cognitive impairment) or a combination of vascular history and neuroimaging data
Intact ADL	Whether ADLs were considered, amount of functional impairment allowed, ADL criteria

Abbreviations: ADL, Activities of Daily Living; CDR, Clinical Dementia Rating; DSM, Diagnostic and Statistical Manual of Mental Disorders; NINDS-AIREN, National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences; VaD, vascular dementia; VCI-ND, Vascular Cognitive Impairment no Dementia

Table 2. The results for the progression of VCI-ND over time in studies, where reported.

Study population (Author, year)	Follow-up time	Progression of VCI-ND			
		Cognitive deterioration, not dementia, %	Dementia, %	Death, %	Improved cognitive function, %
CSHA (Ingles, 2002)	5 years		44		
Osaka-Tajiri Project (Meguro, 2012)	5 years		24	45	
Sydney Stroke Study (Sachdev, 2009)	3 years		24		27
Alzheimer's Centre, Italy (Frisoni, 2002)	40 months	34*		50	
ACCORD Study (Hsiung, 2006)	2 years		40		8
University Medical Centres' stroke patients (Rasquin, 2007)	2 years	30	3		14
Stroke patients (Williamson, 2008)	1 year				45

Abbreviations: ACCORD, Canadian Collaborative Cohort of Related Dementias; CSHA, Canadian Study of Health and Aging; VCI-ND, Vascular Cognitive Impairment no Dementia.

Notes: Data complete where available. *Nursing home placement, functional loss or cognitive deterioration.

Box 1. Proposal for steps to define VCI-ND in research settings

1. Concern regarding a decline in cognitive function

The patient, someone who knows the person well, or a clinician who has observed the person, notices a progressive impairment in their cognitive function.

2. Impairment in one or more cognitive domains

Age and education adjusted cut-offs for cognitive impairment over a wide range of cognitive domains should be investigated, including, but not limited to executive function, attention and memory, as well as global cognitive function. MCI due to AD should be considered if there are isolated impairments in episodic memories. Examples of appropriate cognitive tests may include the Rey Auditory Verbal Learning Test, the Trail Making Test and the MMSE. However, cognitive tests should be validated in the population being studied.

3. ADLs not affected beyond what is expected for a person's age

ADLs should be unaffected or not affected beyond what would be expected for a person's age. Certain ADLs known to be affected by severe cognitive impairment should not be impaired, such as managing medications or managing money.

4. Exclusion of individuals with dementia

Standardised criteria such as the DSM criteria or NINDS-AIREN criteria for VaD

5. Exclusion of other causes of cognitive impairment

Examples include evidence of Parkinson's disease, MCI due to AD (positive biomarkers for AD as outlined in the MCI due to AD consensus criteria [1]) or dementia with Lewy bodies

6. Evidence of a vascular cause based on NINDS-AIREN criteria for VaD as follows:

- "*Cerebrovascular disease*, defined by the presence of focal signs on neurologic examination, such as hemiparesis, lower facial weakness, Babinski sign, sensory deficit, hemianopia, and dysarthria consistent with stroke (with or without history of stroke), and evidence of relevant CVD by brain imaging (CT or MRI) including *multiple large vessel infarcts* or a *single strategically placed infarct* (angular gyrus, thalamus, basal forebrain, or PCA or ACA territories), as well as *multiple basal ganglia* and *white matter lacunes*, or *extensive periventricular white matter lesions*, or combinations thereof" [2]
- There should be a relationship between the cognitive impairment and the vascular cause such as the cognitive impairment should not have been present before a stroke and should be present within 3 months of the stroke or sudden onset or stepwise progression of cognitive impairment.

7. Probable or possible VCI-ND

Fulfilling the above criteria would result in a case of probable VCI-ND. The term possible VCI-ND may be used in cases where there is cognitive impairment, but the relationship between the vascular cause and cognitive impairment cannot be readily identified, or neuroimaging studies are not available to show cerebrovascular disease, and other possible causes of cognitive impairment (e.g., AD pathology) can be ruled out.

8. CIND with AD and vascular pathology

Evidence of multiple causes of cognitive impairment such as AD pathology beyond that expected for a person's age and vascular pathology should be identified as "CIND with AD and vascular pathology"

9. More accessible criteria for healthcare providers

Where advanced neuroimaging is not available, a focus should be on clinical features for diagnosis. This should include no diagnosed dementia, cognitive impairment after stroke or previous history of vascular disease with sudden onset or stepwise progression of cognitive impairment, without impairment of episodic memory and ADLs unaffected or mildly affected to identify possible VCI-ND.

Abbreviations: AD, Alzheimer's disease; ADL, activities of daily living; CIND, cognitive impairment-no dementia; DSM, Diagnostic and Statistical Manual of Mental Disorders; MCI, mild cognitive impairment; NINDS-AIREN, National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences; VCI-ND, Vascular Cognitive Impairment no Dementia.